REMARKS

In the Final Action dated March 20, 2002, claims 1-5 and 24-32 are pending and are under consideration. Claims 1-5 and 24-28 are rejected under 35 U.S.C. §102 (e) as allegedly anticipated by Kamb (U.S. Patent 5,869,242). Claims 1-7 and 24-30 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Sutherland et al. (U.S. Patent 5,985,619). Claims 1-5, 10, 14 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster (U.S. Patent 6,074,823). Claims 1-5, 8-9, 11-13, 24-28 and 31-32 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Caprioli (U.S. Patent 5,808,300). Claims 1-5, 10, 14, 16 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in the view of Sutherland et al. Claims 1-5, 8-9, 11-13, 15, 24-28 and 31-32 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Caprioli and further in view of Sutherland et al. Claims 1-5, 10, 14, 16-18 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in view of Caprioli.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance or at least in better condition for appeal. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 1-5 and 24-28 are rejected under 35 U.S.C. §102 (e) as allegedly anticipated by Kamb (U.S. Patent 5,869,242).

It is observed that claims 1-5 and 24-28 are directed to methods of detecting a difference of one or more nucleotides between a nucleic acid molecule and a reference nucleic acid molecule. The claimed methods involve subjecting the test nucleic acid to base-specific

cleavage and separating the resulting oligonucleotide fragments based on mass by MALDI-TOF MS to produce a fingerprint.

Applicants previously submitted that Kamb's disclosure relates to a method of mutation detection based on analysis of nucleic acid molecules by mass spectrometry. In one instance, Kamb discloses cleaving the amplified fragment of a test molecule with a restriction enzyme (i.e., sequence-specific cleavage) prior to mass spectrometry. However, Kamb does not teach a method of detection that employs base-specific cleavage of a test nucleic acid molecule, as instantly claimed.

The Examiner is of the opinion that the method employing cleavage by a restriction enzyme is merely a preferred embodiment of Kamb. The Examiner argues that the teaching of Kamb is not limited to this preferred embodiment. Furthermore, the Examiner states: "[a]lthough Kamb reference uses "sequence-specific cleavage", the property of 'base specific cleavage' is inherently present in this chemically and structurally identical molecule." The Examiner seems to be saying that sequence-specific cleavage is inherently base-specific. The Examiner also argues that the term "base-specific cleavage", as recited in the instant claims, given the broadest reasonable interpretation consistent with the specification, is interpreted to include cleavage by restriction enzymes.

In response, Applicants respectfully submit the following respecting the Kamb reference. In the first instance, Kamb teaches a method of detecting a mutation where no cleavage is involved at all (see col.5, example III of Kamb). Kamb admits that such detection method would not be effective if the mutation is simply a change of a base, as opposed to an insertion or deletion of a base. However, Kamb discloses that if a change of base in a test molecule results in a change in the recognition site of a restriction enzyme, such base change

(i.e., mutation) can be detected by first cleaving an amplified fragment of the test molecule with the restriction enzyme. See col. 6 of Kamb. The restriction enzyme recognizes either the mutant or the wild-type sequence. Therefore, upon cleavage by the restriction enzyme, the mutant molecule generates a signature mass spectrum distinct from that of the wild type. Such a procedure disclosed by Kamb is in effect limited to detection where the mutation or its surrounding sequence is known. Kamb does not teach how to detect a mutation that does not change any restriction site. In contrast, the claimed methods require no prior knowledge of sequence and do not depend on cleavage at the site of a mutation. Moreover, restriction enzymes act upon specific strings of sequences, i.e., cleavage by a restriction enzyme is sequence specific. Unlike base-specific cleavage by an agent (e.g., uracil-N-glycosylase) that cleaves a nucleic acid molecule at each occurrence of a particular base, cleavage by restriction enzymes is not base-specific.

Applicants further submit that base-specific cleavage, as taught by the present invention, results in a more efficacious and accurate detection of nucleotide differences as compared to a detection achieved by a method involving sequence-specific cleavage. In particular, multiple restriction enzymes would be required in order to fully characterize the changes in bases in a particular fragment, as there is likely to be regions of DNA which are devoid of sites for restriction enzymes. In contrast, with base-specific cleavage, in effect only four separate enzymes would be required in order to digest a single base at a time in order to determine the sequence of a particular location. A single base-specific enzyme is likely to be highly effective anywhere in the DNA to generate a small enough fragment in order to be analyzed by MALDI-TOF.

It is further observed that Kamb teaches that a mutation can be detected by cleaving the amplified fragment of a test molecule with an exonuclease. See col. 8, Example V. At col. 10, lines 48 to 51, Kamb states that digestion of samples may be achieved by using enzymes or simply by chemical cleavage. However, Kamb makes no mention of base specific cleavage.

The Examiner also points out that Kamb teaches that nucleic acids can be digested with uracil-N-glycosidase at column 4, lines 39-41.

In this regard, Applicants respectfully submit that it is not clear to Applicants how the Examiner is relying upon the referenced passage in Kamb in rejecting the instant claims as allegedly anticipated. Specifically, Applicants respectfully point out that the Examiner admits at page 4, line 9 of the Final Action in the context of a §103 rejection, that Kamb does not teach a method of detection wherein the base specific cleavage is uracil-specific and mediated by uracil-N-glycosylase.

In any event, Applicants submit that the reference to uracil-N-glycosylase in Kamb does not constitute a teaching of base-specific cleavage for the purpose of detecting mutations in a test nucleic acid molecule. Specifically, it is observed that Kamb states at col. 4, lines 39 to 41:

> "One useful substitution is to incorporate deoxyuridine into amplified DNA. This is useful for producing small fragments by later digesting the amplified DNA with uracil-N-glycosidase."

However, Kamb does not teach how uracil-N-glycosylase comes into play in a method of detecting mutations. Considering the reference as a whole, the text is equivocal to one skilled in the art in that uracil-N-glycosylase may be used for cleavage only when a mutated DNA molecule differs from the wild type molecule by a thymine/uracil. Alternatively, the text

may be suggesting the use of uracil-N-glycosylase/uracil to reduce amplification artifacts during PCR, as described in Sutherland et al. (below).

In this regard, Applicants respectfully submit that the prior art must provide an enabling disclosure of how to make and use the claimed subject matter for anticipation purposes. Scripps Clinic & Research Foundation v. Genetech, Inc., 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991). Applicants respectfully submit that neither those specific passages of the Kamb patent referenced by the Examiner, nor the entire disclosure of Kamb, provides an enabling teaching for a method of detection using uracil-specific cleavage or any base-specific cleavage.

In view of the foregoing, Applicants respectfully submit that the Kamb reference does not teach the present invention. Withdrawal of the rejection of claims 1-5 and 24-28 under 35 U.S.C. §102 (e) as allegedly anticipated by Kamb is therefore respectfully requested.

Claims 1-7 and 24-30 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Sutherland et al. (U.S. Patent 5,985,619) (November 16, 1999).

The Examiner admits that Kamb does not teach a method of detection wherein the base specific cleavage is uracil-specific and mediated by uracil-N-glycosylase. However, the Examiner points out that Sutherland et al. teach a method wherein the base-specific cleavage is uracil-specific and mediated by uracil-N-glycosylase (column 9, lines 4-29). The Examiner contends that one skilled in the art, by employing scientific reasoning, would have utilized the uracil-specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. in the mass spectrometry to assess DNA sequence polymorphisms taught by Kamb in order to improve the sequencing of nucleic acids containing unconventional bases. The Examiner further contends that one skilled in the art would have been motivated to do so in order to achieve the express

advantages noted by Sutherland et al., namely, uracil-N-glycosylase (UNG) is commercially available and is useful to specifically cleave uracil.

Applicants respectfully submit that it is improper for the Examiner to reject the instant claims on the ground that one skilled in the art would have combined the teaching of Kamb with that of Sutherland et al. by "employing scientific reasoning." The motivation for combining these references is missing on this record.

Applicants respectfully submit that Sutherland et al. merely teach the availability of uracil-N-glycosylase as a uracil-specific cleavage enzyme. Sutherland et al. do not provide any teaching or suggestion for those skilled in the art to use uracil and uracil-N-glycosylase in a method of detecting nucleotide differences.

The Examiner has identified certain "express advantages" of Sutherland et al. Applicants are presently unaware of the relevance of the alleged advantages. Assuming, pro arguendo, the existence and relevance of such advantages, Applicants submit that these advantages alone provide no motivation for those skilled in the art to modify the Kamb method. In this regard, Applicants submit that the suggestion or teaching to combine the references must be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Furthermore, the Examiner argues that the Kamb reference provides an enabling methodology and evidence a number of different restriction enzymes including uracil-N-glycosylase. Again referencing col. 4, lines 36-46 of Kamb, the Examiner states that uracil-N-glycosylase was actually experimentally studied and found to be functional.

Applicants reassert that the disclosure of Kamb at col. 4, lines 36-46, is unclear and ambiguous. As discussed above in connection with the §102 rejection, the quoted passage of

Kamb does not constitute a teaching of a method of detection using uracil-N-glycosylase or any base-specific cleavage. Applicants respectfully submit that the Examiner has used the aid of hindsight in evaluating the present invention to support an incorrect finding of obviousness under 35 U.S.C. §103. It is impermissible to first ascertain factually what an inventor did and then view the prior art in such a manner as to select random bits and pieces of that art to reconstruct Applicants' invention. See, In re Shuman, 361 F.2d 1008, 1012, 150 U.S.P.Q. 54, 57 (CCPA 1966).

Accordingly, it is respectfully submitted that the rejection of claims 1-7 and 24-30 under 35 U.S.C. §103 (a) based on the combination of Kamb and Sutherland et al. is improper. Withdrawal of the rejection is therefore respectfully requested.

Claims 1-5, 10, 14 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster (U.S. Patent 6,074,823).

The Examiner admits that Kamb does not teach the method of using a computer capable of controlling a method of detecting mutation by MALDI-TOF MS. However, the Examiner contends that Koster teaches a method of using a computer capable of controlling a method of detecting mutation by MALDI-TOF MS (column 5, lines 22-35).

As submitted above, Kamb does not teach or suggest a method of detection involving base-specific cleavage, as instantly claimed. This deficiency is not cured by the Koster reference. Thus, the claimed methods of detection involving base-specific cleavage and a computer capable of controlling a method of detecting mutation by MALDI-TOF MS, are not taught or suggested by the Kamb reference and the Koster reference, taken individually or in combination. Accordingly, the rejection of the claims under 35 U.S.C. §103 (a) over Kamb in view of Koster, is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 1-5, 8-9, 11-13, 24-28 and 31-32 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Caprioli (U.S. Patent 5,808,300).

The Examiner admits that Kamb does not teach the method of subjecting fragmentation products to further separation by the post-source-decay method. However, the Examiner contends that Caprioli teaches a method of subjecting fragmentation products to further separation by a post-source-decay method (column 3, lines 9-11).

Applicants first submit that Caprioli teaches the application of a post-source-decay method in separating peptides, but not oligonucleotides involved in the claimed methods. There is no teaching or suggestion in Caprioli as to whether the method of the post-source-decay method disclosed by Caprioli can be successfully applied in separating oligonucleotide fragments resulting from base-specific cleavage. Furthermore, Applicants submit that neither Kamb nor Caprioli, nor the combination of the two, teach or suggest a method of detection involving base-specific cleavage, as instantly claimed. Accordingly, the claimed methods of detection involving base-specific cleavage and subjecting oligonucleotide fragments to further separation by a post-source-decay method, are not taught or suggested by the Kamb reference and the Caprioli reference, individually or in combination. Therefore, withdrawal of the rejection under 35 U.S.C. §103 (a) over Kamb in view of Caprioli, is respectfully requested.

Claims 1-5, 10, 14, 16 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in the view of Sutherland et al.

The Examiner admits that Kamb and Koster taken together do not teach a method wherein the cleavage is uracil-specific and mediated by uracil-N-glycosylase. According to the Examiner, those skilled in the art would have applied the uracil specific base cleavage mediated by uracil-N-glycosylase, as taught by Sutherland et al., in the computerized mass spectrometry to

assess DNA sequence polymorphisms as taught by Kamb in view of Koster. The Examiner contends that those skilled in the art would have done so after "employing scientific reasoning" and because Sutherland et al. suggest the advantages of uracil-N-glycosylase.

Applicants respectfully reassert that Sutherland et al. merely teach the availability of uracil-N-glycosylase as a base-specific cleavage enzyme. Sutherland et al. do not teach or suggest utilizing the uracil base and uracil-N-glycosylase in a method of detecting nucleotide differences as taught by Kamb. The advantages allegedly provided by Sutherland et al., i.e., that uracil-N-glycosylase (UNG) is commercially available and is useful to specifically cleave uracil, are irrelevant and provide no motivation for those skilled in the art to modify the Kamb method. Accordingly, the Examiner's rejection of the instant claims based on the combination of Kamb, Koster and Sutherland et al. is improper. Therefore, withdrawal of the rejection under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in the view of Sutherland et al., is respectfully requested.

Claims 1-5, 8-9, 11-13, 15, 24-28 and 31-32 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Caprioli and further in view of Sutherland et al.

The Examiner admits that Kamb and Caprioli taken together do not teach a method wherein the cleavage is uracil-specific and mediated by uracil-N-glycosylase. However, the Examiner contends that Sutherland provides such teaching and motivation for those skilled in the art to modify the method as taught by Kamb and Caprioli.

As submitted above, Sutherland et al. merely teach the availability of uracil-N-glycosylase as a base-specific cleavage enzyme. Sutherland et al. do not teach or suggest utilizing the uracil base and uracil-N-glycosylase in a method of detecting nucleotide differences as taught by Kamb. Neither do Sutherland et al. provide any motivation for those skilled in the

art to modify the Kamb method. Accordingly, the Examiner's rejection of the instant claims based on the combination of Kamb, Caprioli and Sutherland et al. is improper. Therefore, withdrawal of the rejection under 35 U.S.C. §103 (a) over Kamb in view of Caprioli and further in the view of Sutherland et al., is respectfully requested.

Claims 1-5, 10, 14, 16-18 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in view of Caprioli.

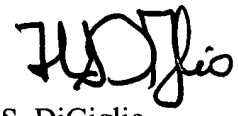
The Examiner admits that Kamb in view of Koster does not teach a method of subjecting the fragments to further separation by post-source-delay method. However, the Examiner contends that such teaching is provided by Caprioli. The Examiner further argues that those skilled in the art would have been motivated to combine and substitute a further separation by post-source-decay method of Caprioli into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of Koster in order to achieve the express advantages, as noted by Caprioli, of a method which is used in order to obtain sequence verification.

Applicants respectfully submit that Caprioli does not teach or provide a suggestion as to whether post-source-decay method disclosed by Caprioli can be successfully applied in separating oligonucleotide fragments resulting from base-specific cleavage. Furthermore, Applicants submit that Kamb and Koster, taken together, do not teach or suggest a method which involves base-specific cleavage, as discussed above. Such deficiency is not cured by the Caprioli reference. Thus, the three cited references, Kamb, Koster and Caprioli, either taken individually or in combination, do not teach or suggest the instantly claimed methods which employ base-specific cleavage and post- source-decay for separating oligonucleotide fragments. Accordingly, the rejection of claims 1-5, 10, 14, 16-18 and 24-28 under 35 U.S.C. §103 (a) over Kamb in view

of Koster and further in view of Caprioli, is overcome. Withdrawal of the rejection is therefore respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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